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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

STANLEY

Group Art Unit: 1655

Appln. No.: 09/760,819

Examiner: LU, F.

Filing Date: January 17, 2001

For: **USE OF NUCLEIC ACIDS BOUND TO CARRIER MACROMOLECULES**

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June 4, 2002

RESPONSE AND AMENDMENT UNDER 37 C.F.R. § 1.111

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Responsive to the outstanding Office Action mailed December 4, 2001, kindly consider and enter the following amendments and remarks.

IN THE CLAIMS:

Kindly enter the following amended claims.

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1. (Amended) A process for the replication of a nucleic acid template comprising

B1

bonding a primer having a sequence complementary to a portion of a nucleic acid template to a carrier macromolecule that does not inhibit DNA polymerase activity;

hybridizing the bound primer to said template; and

B1 extending said primer to replicate said template in complementary form.

18. (Amended) A method of detecting the presence of a nucleic acid bound to a carrier macromolecule comprising:

providing a first nucleic acid bound to a carrier macromolecule that does not inhibit

B2 DNA polymerase activity;

providing a second nucleic acid bound to a carrier macromolecule that does not inhibit DNA polymerase activity,

contacting said first and second nucleic acids under hybridization conditions, and

detecting hybridization between said first and second nucleic acids.

21. (Amended) An immobilized nucleic acid comprising a nucleic acid bound to a carrier macromolecule that does not inhibit DNA polymerase activity, which macromolecule is itself bound to a solid support.

B3 22. (Amended) A method of using the immobilized nucleic acid as claimed in claim 21 comprising:

formulating the immobilized nucleic acid as a primer or as a hybridization probe and

introducing the immobilized nucleic acid into a reaction utilizing a primer or a hybridization probe.

REMARKS

Reconsideration and allowance of the pending claims are requested in view of the preceding amendments and following remarks.

Claims 1-22 are pending in the instant application. Claims 1, 18, 21 and 22 have been rewritten for the purposes of clarification. Support for the amendments to the claim 1 can be found throughout the Application as filed, including the original claims. Specific support for the amendments to claims can be found in the specification at, *inter alia*, page 6 and in the Examples. No new matter will be introduced into the application upon entry of these amendments.

The Examiner objects to the application for allegedly failing to refer to the prior application from which priority benefits are claimed. However, the Examiner is incorrect in this regard. Applicant directs the Examiner's attention to Applicant's Request For Filing under Rule 53(b)(1), wherein at section 9, the Patent Office is instructed to amend the specification before the first line to recite that the instant application is a continuation of Application No. 09/313,385, filed 18 May 1999. The Examiner apparently has failed to act on this Preliminary Amendment. Applicant respectfully requests that the Examiner enter the amendment as instructed in the papers filed January 17, 2001.

The Examiner objected to the informal drawings submitted at the time the application was filed. Applicant includes herewith formal drawings addressing the objections set forth in FORM PTO 948. Entry is respectfully requested.

Claims 1-17, 19 and 20 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking the support of an enabling disclosure. The Examiner asserts that the

specification is enabling only for the macromolecule Dextran because there is no predictability as to which macromolecules can be used as a carrier without inhibiting DNA polymerase activity. Specifically, the Examiner suggests that because it is known that both Hb and agarose are potential inhibitors of DNA polymerases, undue experimentation would be required to carry out the claims. *See* outstanding Office Action at pages 3 and 4. Applicant traverses this rejection for at least the following reasons.

Page 8 of the instant specification lists numerous carrier macromolecules that may be used to practice the claims. The Examiner has failed to provide evidence as to why a skilled artisan could not employ any of the delineated macromolecules in lieu of Dextran. Instead, the Examiner seeks to impermissibly restrict Applicant to the macromolecule utilized in the exemplified preferred embodiments.

The Examiner asserts that a skilled artisan would be directed to employ a carrier macromolecule that is incompatible with DNA polymerase activity, such as agarose. Applicant points out that the skilled artisan is not imputed to have a deficit of common sense, and will select macromolecules suitable for interaction with the reagents necessary to practice the claims. For example, it is well known to those of average skill in the art that ultrapurified agarose that does not inhibit DNA polymerase is commercially available, and that such purified agarose should be selected over cruder forms of agarose for practicing the claims. Thus, a skilled artisan has the capacity to select macromolecular carriers that do not impair the enzymatic processes required to achieve the preferred embodiments of the invention.

Nevertheless, in an effort to expedite to further prosecution on the merits, Applicants respectfully submit that the claims now recite a process for the replication of a nucleic acid

template, comprising bonding a primer having a sequence complementary to a portion of a nucleic acid template to a carrier macromolecule that does not inhibit DNA polymerase activity; hybridizing the bound primer to said template; and extending said primer to replicate said template in complementary form. The claims are enabled as written. Applicant respectfully submits that the Section 112(1)-based rejection should be withdrawn.

Claims 20 and 22 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, although the reasons expressed by the Examiner for issuing this rejection are garbled, and not completely understood by Applicant. The Examiner appears to be confused about the intended meaning of claim 20. In particular, the Examiner does not understand the plain English meaning of the term "therefrom" as used in claim 20, and queries whether Applicant intends to mean claim 20 to recite "therefore". Claim 22 was rejected for reciting the European style "use" claim, which fails to recite active steps. Applicant traverses this rejection for at least the following reasons.

With respect to the term "therefrom", the Examiner's question "[d]oes the phrase therefrom" mean "therefore" or something else?" is not well taken. *See* outstanding Office action at page 5. Applicant has written exactly what is intended, and implores the Examiner to research words not understood before wasting Applicant's resources educating the Examiner on the use of common terms in the English language. Since the Examiner has expressed on the record an unfamiliarity with the distinct meanings of the words "therefore" and "therefrom", the Examiner is invited to read the attached dictionary definitions of these terms, which Applicant has supplied for the Examiner's convenience. The term "therefrom"

continues to be Applicant's word of choice in claim 20, and Applicant asserts claim 20 is definite as written.

The Examiner rejected claim 22 as being indefinite for not reciting the active steps of a method. Claim 22 now clearly recites a process with active steps in accordance with accepted U.S. patent practice.

In view of the above, Applicant respectfully submits that claims are definite, and that the Section 112(2)-based rejection of the claims should be withdrawn.

Claim 22 was rejected under 35 U.S.C. § 101 for failing to recite subject matter in proper process format. Applicant has amended original "use" claim 22 to better conform to preferred U.S. patent practice. Withdrawal of this Section 101-based rejection is respectfully requested.

Claims 1-6, 8, 9, 11, 13, 17, 21 and 22 were rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 5,814,445 to Belyavsky et al. (hereinafter Belyavsky '445). The Examiner asserts that Belyavsky '445 teaches the precipitation of DNA fragments that are bound to glycogen and used as targets for polymerase chain reaction (PCR) amplification, not as primers. *See* outstanding Office Action at page 6. The Examiner alleges that when primers bind to the target, they become indirectly bound to the glycogen "carrier", and, thus, meet the requirements of claim 1. *Id.* Applicant traverses for at least the following reasons.

The Examiner's analysis of Belyavsky '445 is technically inaccurate and misconstrues the facial meaning of the claims. Fundamentally, Belyavsky '445 provides for a process in which glycogen is absent during PCR steps. Belyavsky '445 (at column 8) teaches the ethanol precipitation of DNA from solution using 96 percent ethanol and glycogen as a "carrier".

Glycogen is employed in this process step to produce steric exclusion of DNA in order to facilitate precipitation by increasing the effective concentration of the DNA in solution in the presence of an organic solvent. Contrary to the Examiner's assertions, DNA is not bound to glycogen, and there is no teaching that DNA bound to glycogen is subjected to PCR amplification.

Claims 1-20 recite a process for the replication of a nucleic acid template comprising hybridizing to the nucleic acid template a primer having a sequence complementary to a portion of said template. Prior to hybridization, the primer is bound to a carrier macromolecule that does not inhibit DNA polymerase activity. Following hybridization, the primer is then extended to replicate the nucleic acid template in a complementary form.

Claim 21 recites an immobilized nucleic acid comprising nucleic acid bound to a carrier macromolecule, the carrier macromolecule itself being bound to a solid support. The Examiner admits that Belyavsky '445 "did not directly show that glycogen (macromolecule) was bound to a solid support as recited in claims 21 and 22". *See* outstanding Office Action at page 6. The Examiner asserts that Belyavsky '445 inherently teaches bonding to a "solid support" insofar as DNA fragments and glycogen were known to be pelleted onto the bottom of a centrifuge tube.

Applicants find no support in Belyavsky '445 for such allegations. The Examiner's facile logic is plainly inadequate, as physically pelleting DNA and glycogen in a glass tube is not a bonding process. To the contrary, centrifuge tubes are generally designed to be inert to avoid bonding to the materials introduced to the tubes. The Examiner is invited to explain how the pelleted material of Belyavsky '445 would react with a glass centrifuge tube to form

a bond, and to explain where the cited reference teaches this step. Moreover, Belyavsky '445 fails to teach nucleic acid bound to a carrier macromolecule, as the DNA of this reference is not bound to glycogen. Glycogen is employed in this process step to produce steric exclusion of DNA, thereby reducing the "space" in which the nucleic acid may remain in solution. Glycogen, therefore, facilitates precipitation without bonding with the DNA.

Since Belyavsky '445 does not teach bonding a primer to a carrier macromolecule that does not inhibit DNA polymerase activity, and then hybridizing the bound primer to a nucleic acid template, Belyavsky '445 fails to disclose each and every element of the claimed process. Likewise, Belyavsky '445 fails to teach an immobilized nucleic acid comprising nucleic acid bound to a carrier macromolecule, the carrier macromolecule itself being bound to a solid support. Therefore, a *prima facie* case of anticipation has not been established. Applicant respectfully submits that the claims are allowable over Belyavsky '445, and that this Section 102-based rejection of claims 1-6, 8, 9, 11, 13, 17, 21 and 22 should be withdrawn.

Claims 1, 4, 6, 8, 9, 11, 12, 15, 21 and 22 were rejected 35 U.S.C. § 102(e) as being anticipated by a 1993 BioTechniques article authored by Lee *et al.* (hereinafter Lee 1993). The Examiner asserts that since Lee 1993 teaches DNA sequencing using biotinylated single stranded DNA bound to beads, "the biotin molecule and the bead here could be considered as a carrier macromolecule and a solid support respectively as recited in claims 1 and 12". *See* outstanding Office Action at page 7. The Examiner also asserts that "since a sequencing primer annealed with biotinlyated single-stranded DNA in sequencing reaction [sic], the

primer could be considered to indirectly bind to the carrier macromolecule as recited in claim 1". *See id.* Applicant traverses for at least the following reasons.

Applicant notes that biotin is not a macromolecule as understood in the art of molecular biology. Biotin is a C_{10} single molecule that lacks any repeating unit structure and has a molecular weight of only 224. Macromolecules are commonly defined to be "a very large molecule, such as a polymer or a protein, consisting of many smaller structural units linked together". *See* attached *American Heritage* dictionary definition. The preferred macromolecules of the claims have a peak molecular weight range of 1,000 to 40,000,000, an exemplary range substantially greater than the molecular weight of biotin. Applicants simply find no basis in the general knowledge of the art for the Examiner's naked assertion that biotin constitutes a macromolecule.

Moreover, the DNA of Lee 1993 that is immobilized via biotin onto beads is not a primer, but a PCR target. The claims are directed to a primer bound to a carrier macromolecule that does not inhibit DNA polymerase activity. Thus, in this respect, the Examiner's argument for the rejection based on Lee 1993 suffers from the same deficiency as was set forth in the rejection over Belyavsky '445.

Claims 1-20 recite the replication of a nucleic acid template comprising hybridizing to the template a primer having a sequence complementary to a portion of said template. Prior to hybridization, the primer is bound to a carrier macromolecule that does not inhibit DNA polymerase activity. Following hybridization, the primer is then extended to replicate the nucleic acid template in a complementary form. Claim 21 recites an immobilized nucleic

acid comprising nucleic acid bound to a carrier macromolecule, the carrier macromolecule itself being bound to a solid support.

For the reasons given above, Lee 1993 fails to disclose each of the features recited in the claims, and, therefore, cannot anticipate the claimed embodiments of the invention. Applicant respectfully submits that this Section 102-based rejection of the claims should be withdrawn.

Claims 1, 4, 6, 8, 9, 11, 15, 17-19, 21 and 22 were rejected 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,652,099 to Conrad (hereinafter, Conrad '099). The Examiner states that Conrad '099 discloses a poly(AC) template amplified using a biotinylated synthetic 22-mer primer, and that hybridization between biotinylated poly(AC) and fluorescence labeled poly (FC) probes were detected by quenched fluorescence of the poly (FC) probe. The Examiner asserts that biotin serves as a carrier macromolecule and a detectable marker, and that hybridization between biotinylated poly(AC) probes and fluorescence labeled poly(FC) probes immobilized on avidinylated beads reads on claims 21 and 22. *See* outstanding Office Action at page 8. Applicant traverses for at least the following reasons.

The Examiner points to column 27 for support of this assertion of anticipation by Conrad '099. However, column 27 of Conrad '099 merely teaches the use of biotinylated primers to produce amplimers having the sequence $^{5'}$BIOTIN-poly(TG)$^{3'}$. Nucleic acid probes may be mixed with these biotinylated amplimers, forming hybrids, and the hybrids may then be adsorbed via the $^{5'}$BIOTIN moiety to avidinylated beads. Applicant does not find any teaching at column 27 directed to a nucleic acid primer bound to a carrier

macromoleule that does not inhibit DNA polymerase activity, the carrier macromolecule itself being bound to a solid support. Suitable macromolecules according to the claims preferably have a peak molecular weight ranging from 1,000 to 40,000,000. As noted above, biotin has a molecular weight of only 224, which is not sufficient for delineating biotin as macromolecule.

Thus, Conrad '099 is silent with respect to the claimed immobilized nucleic acid bound to a carrier macromolecule that does not inhibit DNA polymerase activity, which macromolecule is itself bound to a solid support. This reference is also lacking insofar as it does not disclose a process for the replication of a nucleic acid template, the process comprising bonding a primer having a sequence complementary to a portion of a nucleic acid template to a carrier macromolecule that does not inhibit DNA polymerase activity; hybridizing the bound primer to said template; and then extending said primer to replicate said template in a complementary form. Applicant respectfully submits that Conrad '099 fails to teach each and every element of the claims, and, therefore, the Section 102-based rejection over this reference should be withdrawn.

Claim 16 was rejected 35 U.S.C. § 103(a) as being unpatentable over Conrad '099, in view of U.S. Patent No. 5,538,871 to Nuovo *et al.* (hereinafter Nuovo '871). The Examiner asserts that Conrad . Applicant traverses for at least the following reasons.

Claim 16 recites a process comprising bonding a primer having a sequence complementary to a portion of a nucleic acid template to a carrier macromolecule that does not inhibit DNA polymerase activity; hybridizing the bound primer to said template; and then extending said primer to replicate said template in a complementary form, wherein the

extension of the primer is conducted *in situ* in a biological sample. The Examiner asserts that Conrad '099 teaches all of claim 16, except *in situ* extension of a primer. The Examiner attempts to supplement this deficiency of Conrad '099 by also citing Nuovo '871. *See* outstanding Office Action at pages 8-9.

As explained above, Conrad '099 does not teach a process for replicating a nucleic acid template, in which process a primer is bound to a carrier macromolecule that is then hybridized to a nucleic acid template. Nuovo '871 fails to overcome the deficiencies of Conrad '099, as Nuovo '871 merely teaches the production of labeled PCR products via withholding at least one PCR reagent from the PCR milieu until a heating temperature of 50°C to 80°C has been achieved. The combination of Conrad '099 and Nuovo '871 does not even hint at a carrier macromolecule-bound primer having a sequence complementary to a portion of a nucleic acid template, such that the bound primer hybridizes to the nucleic acid template, as this combination of references fails to recognize the importance of employing macromolecules in a process of replicating a nucleic acid template.

The Examiner has the initial burden of presenting a *prima facie* case of obviousness when making a Section 103 rejection. In Re Rijckaert, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). A *prima facie* case of obviousness is established if the prior art suggested to one of ordinary skill in the art to modify the prior art in such a fashion as to produce the claimed invention, and that such a modification would reasonably have been expected to succeed. In Re Dow Chemical, 5 U.S.P.Q. 1529, 1531 (Fed. Cir. 1988).

As discussed above, the hypothetical combination of references is silent with respect to the claimed process, and fails to even hint at the use of primers bound to macromolecules

in a process for the replication of nucleic acid templates. The combination of art provides no suggestion to modify the teachings of Conrad '099 in view of Nuovo '871, or that such a hypothetical combination of teachings would be expected to result in the claimed subject matter. Applicant respectfully submits that, in view of the above, the Examiner has failed to present a *prima facie* case of obviousness under 35 U.S.C. §103. Applicant respectfully submits that claim 16 is allowable over the cited art, and that this Section 103-based rejection should be withdrawn.

The Examiner has rejected claims 1-20 under the judicially created doctrine of obviousness-type double patenting in view of claims 1-15 of U.S. Patent No. 6,207,385. Applicant requests that this rejection be held in abeyance until such time as the Applicants and the Examiner agree upon allowable claim language. Upon receiving indication that the claims are allowable, Applicant will file a terminal disclaimer, if necessary.

Having addressed each of the foregoing rejections or objections, Applicant respectfully submits that this application is now in condition for allowance. Notification to that effect is earnestly solicited.

Should questions relating to patentability of the claims remain, the Examiner is invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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Enclosure: Appendix, Dictionary definitions, Drawings.